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EXAMINER	
PIHONAK, SARAH MAUREEN	
ART UNIT	PAPER NUMBER
4121	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,385	METTLER, HANSPETER	
	Examiner	Art Unit	
	SARAH PIHONAK	4121	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 (national stage application) of PCT/EP2004/011971.

1. Claims 1-23 are pending.

2. Claims 1-23 are rejected.

35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,878,665 in view of EP 1176135. (provided by Applicant on the IDS of 4-24-06).

4. Regarding instant claim 1:

US '6,878,665 patent (known hereafter as US '665) discloses a transition metal chiral catalyst that can be used for asymmetric hydrogenation. Claim 11 of '665 (page 14, column 26) teaches that the transition metal may be ruthenium, while claim 9 (page 14, column 25) teaches that the ligand attached to the ruthenium center is Fluoxphos. Claim 16 of '665 broadly states that the asymmetric hydrogenation is performed on a substrate, and Table 1, pages 10-12

displays examples of substrates. Of particular interest is the hydrogenation of ethyl 4,4,4-trifluoro-3-oxobutyrate, on page 12, Table 1.

5. Regarding instant claim 2:

US '665 teaches all of the embodiments of paragraph 4 above, and additionally that the complex contains an alkene (ex. methylallyl, page 5, column 7, line 54), an arene (ex. benzene, page 5, column 8, line 8), a diene (ex. 1, 5-cyclooctadiene, page 9, column 16, lines 60-65), and/or a polar solvent molecule (ex. pyridine, page 5, column 7, line 55).

6. Regarding instant claim 3:

US '665 teaches all of the embodiments of paragraph 4 above, and additionally that the ruthenium-Fluoxphos complex has at least one ligand selected from 1, 5-cyclooctadiene (page 9, column 16, lines 60-65), or p-cymene (page 5, column 8, line 8).

7. Regarding instant claim 4:

US '665 teaches all of the embodiments of paragraph 4 above; furthermore, the hydrogenation is performed in solvents comprised of C_{1-4} alcohols (page 5, column 8, lines 59-60), dimethylformamide (page 5, column 8, line 57), and further solvent additives, such as an acid (page 9, column 16, lines 60-65).

8. Regarding instant claim 5:

US '665 teaches all of the embodiments of paragraph 4 above, and, that the counterion of the ruthenium complex may be Cl^-, Br^-, I^-, BF_4^-, ClO_4^-, PF_6^-, (page 5, column 8, lines 8-10).

9. Regarding instant claim 6:

US '665 teaches all of the elements of paragraph 4 above, and additionally, that the ruthenium complex may be prepared by mixing a complex of formula $[Ru_2Cl_4(benzene)_2]$ with

the Fluoxphos ligand in tetrahydrofuran (page 9, column 16, lines 10-17). The p-cymene ligand may be substituted for the benzene (page 5, column 8, line 8), and tetrahydrofuran fulfills the polar solvent requirement.

10. Regarding instant claim 7:

US '665 discloses all of the elements of paragraph 4 above, with the addition that the asymmetric hydrogenation is performed with a hydrogen pressure range between 1 to 150 bar (page 6, column 9, lines 16-17). This requirement meets the limitations of instant claim 7, in which the hydrogen pressure is in the range of 1 to 60 bar during the hydrogenation.

11. Regarding instant claim 8:

US '665 teaches all of the elements of paragraph 5 above, and that at least one molecule of the ruthenium complex is 1,5-cyclooctadiene (page 9, column 16, lines 60-65), or p-cymene (page 5, column 8, line 8).

12. Regarding instant claim 9:

US '665 teaches all of the elements of paragraph 5 above, and that the hydrogenation reaction can be performed with solvents such as C_{1-4} alcohols (page 5, column 8, lines 59-60), dimethylformamide (page 5, column 8, line 57), and additional solvent additives, such as an acid (page 9, column 16, lines 60-65).

13. Regarding instant claim 10:

US '665 teaches all of the elements of paragraph 6 above, and additionally, the hydrogenation can be performed with solvents such as C_{1-4} alcohols (page 5, column 8, lines 59-60), dimethylformamide (page 5, column 8, line 57), and additional solvent additives, such as an acid (page 9, column 16, lines 60-65).

14. Regarding instant claim 11:

US '665 teaches all of the elements of paragraph 5 above, and also, that the counterion for the complex may be Cl^-, Br^-, I^-, BF_4^-, PF_6^-, ClO_4^- (page 5, column 8, lines 8-10).

15. Regarding instant claim 12:

US '665 teaches all of the elements of paragraph 11 above, and also that, the counterion for the complex may be Cl^-, Br^-, I^-, BF_4^-, ClO_4^-, PF_6^- (page 5, column 8, lines 8-10, and page 9, column 16, example 6a).

16. Regarding instant claim 13:

US '665 teaches all of the embodiments of paragraph 13 above, and also that the counterion of the ruthenium complex may be Cl^-, Br^-, I^-, BF_4^-, ClO_4^-, PF_6^- (page 5, column 8, lines 8-11, and lines 55-64; also page 9, column 16, lines 60-65).

17. Regarding instant claim 14:

US '665 teaches all of the embodiments of paragraph 12, as well as, that the counter ion may be Cl^-, Br^-, I^-, BF_4^-, PF_6^-, or ClO_4^- (page 5, column 8, lines 8-11, and lines 55-64; also page 9, column 16, lines 60-65).

18. Regarding instant claim 15:

US '665 teaches all of the elements of paragraph 5, and additionally, that the ruthenium-Fluoxphos complex can be prepared by combining $[Ru_2Cl_4(cym)_2]$ with the Fluoxphos ligand in a polar solvent (page 9, column 16, example 2). While this example particularly discloses using $[Ru_2Cl_4(benzene)_2]$, p-cymene may substitute for benzene (page 5, column 8, line 8).

19. Regarding instant claim 16:

US '665 teaches all of the elements of paragraph 11 above, and additionally, that a ruthenium-Fluoxphos complex can be prepared by mixing a compound of formula $[Ru_2Cl_4(cym)_2]$ with the Fluoxphos ligand in a polar solvent (page 9, column 16, example 2). While this example discloses the formation of the complex using $[Ru_2Cl_4(benzene)_2]$, p-cymene may substitute for benzene (page 5, column 8, line 8).

20. Regarding instant claim 17:

US '665 teaches all of the embodiments of paragraph 12 above, regarding the formation of the ruthenium complex by mixing a compound of formula $[Ru_2Cl_4(cym)_2]$ with the Fluoxphos ligand (page 9, column 16, example 2). As stated previously, the p-cymene ligand may substitute for the benzene (page 5, column 8, line 8).

21. Regarding instant claim 18:

US '665 teaches all of the embodiments of paragraph 17 above, with regards to the preparation of the ruthenium-Fluoxphos complex by mixing of $[Ru_2Cl_4(cym)_2]$ with the Fluoxphos ligand (page 9, column 16, example 2). The diethylamine counterion can be substituted with either Cl^-, Br^-, I^-, BF_4^-, PF_6^-, ClO_4^- (page 5, column 8, lines 8-11).

22. Regarding instant claim 19:

US '665 teaches all of the elements of paragraph 5 above, and also that, when the hydrogenation is performed with the hydrogen pressure in the range of 1 to 150 bar (page 6, column 9, lines 17-19). This range falls within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant claim 19.

23. Regarding instant claim 20:

US '665 teaches all of the elements of paragraph 11 above, and additionally, that the hydrogenation is performed at a pressure range of 1 to 150 bar (page 6, column 9, lines 17-19). This falls within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant claim 20.

24. Regarding instant claim 21:

US '665 teaches that, when the hydrogenation is carried out in a selection of C1-4 alcohols, dimethylformamide, and additional solvent additives, with the ruthenium complex possessing at least one ligand of an alkene, diene, arene, or polar solvent molecule, the hydrogen pressure is in the range of 1 to 150 bar (page 6, column 9, lines 17-19). This falls within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant claim 21.

25. Regarding instant claim 22:

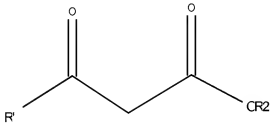
US '665 teaches all of the embodiments of paragraph 17 (regarding instant claim 14), with the additional stipulation that the hydrogenation is performed at a hydrogen pressure range of 1 to 150 bar (page 6, column 9, lines 17-19). This falls within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant claim 22.

26. Regarding instant claim 23:

US '665 teaches all of the embodiments of paragraph 21 above, with the additional stipulation that the hydrogenation is performed at a hydrogen pressure range of 1 to 150 bar (page 6, column 9, lines 17-19). This falls within the hydrogen pressure range of 1 to 60 bar (preferably within 2 to 35 bar) that is specified by instant claim 23.

27. Regarding instant claim 1, US '665 does not teach the following:

Instant claim 1 recites that the ruthenium-Fluoxphos complex is to be used to prepare enantiomerically pure *(S)*- or *(R)*-halo-3-hydroxybutyrates from compounds of the formula shown below:



Formula I

in which R' = CH_2X, CHX_2, or CX_3, with X = Cl, and/or Br

and R2 = C_{1-6} alkyl, C_{3-6} cycloalkyl, aryl, aralkyl, and each aryl or aralkyl may be substituted with one or more C_{1-4} alkyl groups, and/or halogen atoms.

US '665 does not recite in the claims specifically as to the type of substrates that the ruthenium-Fluoxphos catalyst is to hydrogenate. Rather, page 10, column 17, lines 17-19 state "The catalysts according to the invention for stereoselective hydrogenation are useful for carrying out reductions of the following type:", which is followed by examples in Table 1. The substrates shown in Table 1 (pages 10-12) are not just 3-oxobutyrates; some of the chain lengths are longer, or shorter. However, the R2 group of the substrates shown in Table 1 are C_{1-4} alkyl groups, as well as aryl. There are no examples in US '665 in which R2 = C_{3-6} cycloalkyl, aralkyl, or aryl/aralkyl groups optionally substituted with one or more C_{1-4} alkyl groups and/or halogen

atoms. There are also no examples of substrates in which R' = CH_2X, CHX_2, or CX_3, in which X = Cl and/or Br.

28. Instant claim 4 recites that the polar solvents to be used for the hydrogenation are selected from C_{1-4} alcohols, dimethylsulfoxide, dimethylformamide, acetonitrile and mixtures thereof, and possibly further solvent additives. US '665 states that the reaction solvents may be dimethylformamide, C_{1-4} alcohols (page 5 column 8, lines 55 -64), optional solvent additives (page 9, column 16, example 6a, lines 60-62), and other possible polar and non-polar solvents (page 5, column 8, lines 55-64). US '665 does not specifically state that the solvents may be dimethylsulfoxide or acetonitrile.

29. Regarding instant claim 9 - see statement for claim 4 above.

30. Regarding instant claim 10 - see statement for claim 4 above.

31. Instant claim 5 recites that the counterions for the ruthenium-Fluoxphos complex are selected from Cl^-, Br^-, I^-, BF_4^-, PF_6^-, ClO_4^-, OTf, AsF_6^-, and SbF_6^-. US '665 does teach that the counterions for the ruthenium-Fluoxphos complex are possibly Cl^-, Br^-, I^-, BF_4^-, PF_6^-, ClO_4^-, or $NH_2(C_2H_5)_2$, but does not specifically include OTf, AsF_6^-, and SbF_6^- among the selection.

32. Regarding instant claim 11 – see statement for claim 5 directly above.

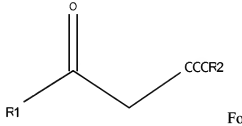
33. Regarding instant claim 12 – see statement for claim 5 directly above.

34. Regarding instant claim 13 – see statement for claim 5 directly above.

35. Regarding instant claim 14 – see statement for claim 5 directly above.

36. Regarding instant claim 1, EP 1176135 (known hereafter as EP '135) discloses the use of a ruthenium complex as a catalyst for asymmetric hydrogenation. The patent application of EP 1176135 was presented in the Information Disclosure Statement submitted by applicant. The

chiral ligand of the ruthenium catalyst is known as SEGPHOS, and is very structurally similar to the Fluoxphos ligand, with the exception that the bis(methylenedioxy)biphenyl moiety is replaced with bis(difluoromethyldioxy)biphenyl. EP '135 discloses the use of the ruthenium-SEGPHOS complex for the asymmetric hydrogenation of ethyl 4-chloroacetoacetoacetate to ethyl *(S)*-4-chloro-3-hydroxybutanoate (pages 9-10, example 6). Additionally, EP '135 teaches that compounds of the formula shown below can undergo asymmetric hydrogenation with the ruthenium-SEGPHOS complex:



Formula II

where R1 = C_{1-15} alkyl group, in which the alkyl group may have one or more substituents selected from hydroxyl, halogen, amino (which may be further substituted with one or more C_{1-4} alkyl groups), benzyloxy, C_{1-4} alkoxy, C_{1-4} alkoxycarbonyl, and aryl groups, among others. R2 may be among the following: C1-8 alkyl, or a benzyl group, which may have one or more substituents (page 11 claim 1).

However, Claim 1 of EP '135 clearly teaches that many of the 4-halo-3-hydroxybutyrates of formula I can undergo asymmetric hydrogenation with the ruthenium-SEGPHOS catalyst. Formula I R' substituents, which may be either CH_2X, CHX_2, and CX_3, (in which X = Cl, and/or Br), are included in the possible R1 groups for formula II. Formula I R2 substituents, which may

be either C_{1-6} alkyl, aryl, or aralkyl (which may be substituted with one or more C_{1-4} alkyl groups, and/or halogen atoms), would be included in the possible R2 substituents of formula II above.

EP '135 does not specifically teach that R2 of formula I may be C_{3-6} cycloalkyl.

37. Regarding instant claim 4:

EP '135 discloses that the preferred solvents for the reaction are protic solvents, such as methanol, ethanol, and isopropanol. It is also taught that the solvents may be mixtures of protic solvents and polar solvents, such as "tetrahydrofuran, toluene, benzene, methyl acetate, ethyl acetate, methylene chloride, and the like" (page 7, lines 21-25). EP '135 does not specifically teach that the hydrogenation should be performed in dimethylsulfoxide or acetonitrile.

38. Highly optically pure *(R)*- and *(S)*- 4-halo-3-hydroxybutyrates are desirable as precursors to pharmaceutical agents. The Fluoxphos ligand of the ruthenium complex as disclosed in US '665 was developed in an attempt to improve both the diastereoselectivity and enantioselectivity of reactions, including asymmetric hydrogenation (US '665 page 2, column 2 paragraphs 2 and 3). The ruthenium-SEGPHOS complex, as disclosed in EP '135, could be used as a catalyst for the asymmetric hydrogenation of a variety of β-keto esters, including various 4-halo-3-oxobutyrates. Therefore, it would be obvious to one skilled in the art to combine the concepts present in US '665 and EP '135, to produce specific enantiomers of 4-halo-3-hydroxybutyrates of formula I because they are desirable as pharmaceutical precursors.

39. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), specifically application No. 03024865.2, filed in the European Patent Office on 10/31/03, which papers have been placed of record in the file.

40. The information disclosure statement (IDS) submitted on 4/26/06 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Thursday 7:00 AM - 5:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

S.P.

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Supervisory Patent Examiner, Art Unit 4121